40. (Withdrawn) The method of claim 32, wherein said thiol-containing compound is N-acetylcysteine or lipoic acid.

REMARKS

In the Office Action mailed July 29, 2008, Claims 1-40 are pending. Claims 1-20, 25-27, 30-31, 36-38 have been withdrawn from further consideration pursuant to **37 CFR 1.142(b),** as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 21 and 32 have been amended. Claims 21-24, 28-29, 32-35, 39-40 were examined as they read on the elected invention and species. Applicant was reminded that even though Claims 28-29 and 39-40 were withdrawn, they were still examined since newly elected N-acetylcysteine (NAC) was recited. Applicant's previous amendments rendered the **112** and **103** rejections of the last Office Action moot, and were therefore withdrawn.

The nonstatutory double patenting rejection for Claims 21-24, 28-29, 32-35 and 39-40; rejection of Claims 28-29 and 29-40 under **35 USC § 112**; and rejection of Claims 21-24, and 33-35 under **35 U.S.C. 103(a)** will be discussed below.

Double Patenting

Claims 21-24, 28-29, 32-35, and 39-40 were provisionally rejected by the Examiner under the doctrine of obviousness-type, double patenting as being unpatentable over Claims 1-5, 8-12 of copending Application No 11/821,221. A Terminal Disclaimer in compliance with **37 CFR 1.32(c)** has been executed by the owner on form PTO/SB/25 (09-08) and the appropriate Terminal Disclaimer fee for a small business entity under **37 CFR 1.20(d)** is included with this response letter.

35 U.S.C. § 112 Rejection:

Applicant's agree that there is insufficient antecedent basis for the limitation of "said thiol-containing compound" in Claims 21 and 32 and do not contest the rejection of Claims 28-29 and 39-40.

35 U.S.C. § 103(a) Rejection:

Claims 21-24, 28-29, 32-35, and 39-40 were rejected under **35 USC 103(a)** as being obvious over McCleary (US Patent Application 2002/0132219 A1) and Medford et al. (US Patent 5,750,351) in view of Applicant's admission of the prior art.

While the Applicant is confident that the Examiner is well acquainted with the requirements necessary to establish a *prima facie* case of obviousness, it is thought prudent to briefly review the required elements. Specifically, in order to meet the burden of establishing a *prima facie* case of obvious, three basic criteria must be met:

1) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. [Note: The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)].

2) Second, there must be a reasonable expectation of success.

3) Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. [Note: The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438

(Fed. Cir. 1991)].

Applicants reject the conclusions presented by the Examiner on the basis that at the time of the claimed invention (1) a person of ordinary skill in the art would not have been sufficiently motivated to combine the teaching of McCleary with the that of Medford and substitute NAC for coenzyme Q10 in combination with CLA for the treating or normalizing hyperlipidemia as Medford does not teach the treatment of hyperlipidemia; (2) at the time of the claimed invention, a person of ordinary skill in the art would not have had a reasonable expectation of success to substitute NAC for coenzyme Q10 in combination with CLA for the treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting as coenzyme and Q10 and NAC are not equivalent antioxidants; and (3) taken as a whole, the prior art reference Medford et al. does not teach the treatment of hyperlipidemia with antioxidants, can not be combined with McCleary and therefore, do not teach or suggest all the claim limitations, specifically hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject.

Applicants have outlined their rationale for this conclusion in the following paragraphs.

The McCleary Application (US Patent Application 2002/0132219A1)

The instant clams are directed to a method for treating or normalizing subcutaneous fat loss or hyperlipidemia coincident with subcutaneous fat loss resulting from anti-retroviral treatment of HIV-1 infection in a subject by administering triglyceride of conjugated linoleic acid (CLA) and N-acetylcysteine (NAC).

McCleary (US Patent Application 2002/0132219A1, hereinafter "McCleary"), as cited by the Examiner, McCleary teaches:

1. [in Abstract] A nutritional supplement composition comprising conjugated linoleic acid (CLA) and coenzyme Q10 for modulating nutrient composition in a human.

2. [¶0002] Hyperlipidemia is disclosed as a disorder due to nutrient partitioning.

3. [¶0006 to 0007] More particularly, it is desirable to provide a means for modulating aberrant pathways of nutrient partitions so as to avoid excessive fat storage, to promote oxidation of fat, and reduce fat levels.

4. [¶0010] McCleary also discloses specifically triglyceride of CLA.

5. [¶0023] McCleary also teaches that fat synthesis and storage are diminished resulting in a fall in the intracellular fat content of the liver, pancreas, and skeletal muscle as well as a fall in visceral fat and total body fat stores accompanied by a decrease in individual fat cell volume. Preferred amounts for CLA are 50 mg to 20 g and for alpha-lipoic acid are 25 mg to 2 g (Table 1).

Medford et al. (US Patent 5,750,351) herein Medford

As cited by the Examiner, "Medford et al. teach that activation of the transcriptional factor NF-kB is linked to hyperlipidemia." Further, the Examiner states, "Importantly, activation of NF-kB can be inhibited by **antioxidants** such as N-acetylcysteine (Col. 2, lines 6-14)." And concludes, "It would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted coenzyme Q10 in the composition as taught by McCleary with N-acetylcysteine as taught by Medford." Concluding, the Examiner infers, "A person of ordinary skill in the art would have been motivated to make this substitution because: (1)

of the **functional equivalence** of both coenzyme Q10 and N-acetylcysteine as well-known antioxidants; and (2) both McCleary and Medford are aimed at treating hyperlipidemia. Therefore, one of ordinary skill in the art would have a reasonable expectation of success in treating hyperlipidemia with a composition comprising a conjugated linoleic acid and the antioxidant N-acetylcysteine."

Consideration of Examiner's conclusions:

Conclusion – Meford teaches activation of transcriptional regulatory factor NF-kB is linked to hyperlipidemia.

Response - While, it can be inferred that Medford et al. teach that activation of the transcriptional factor NF-kB is linked to hyperlipidemia, the linkage described by Medford et al. is "causative" and not resultant (Figure 1). That is to say, Medford et al. teach that hyperlipidemia, in combination with other "risk factors" such as smoking, may "cause" NF-kB activation resulting in atherosclerosis, but hyperlipidemia is not a result of NF-kB activation. Just as smoking is also given as an example of a risk factor that may cause activation of NF-kB and result in atherosclerosis [¶0010 Medford]. The teaching of Medford is to treat atherosclerosis through the inhibition of VCAM-1, which is translationally expressed only on the surface of vascular cells via activated NF-kB resulting from a combination of risk factors including hyperlipidemia. It was not the objective of Medford, nor does Medford teach, the treatment of hyperlipidemia anymore than Medford teaches the treatment of smoking, diabetes or hypertension.

Further, the teaching of Meford is limited to endothelial cells capable of expressing VCAM-1, while it is well-known by a person of ordinary skill in the art that hyperlipidemia is the result of enhanced hepatic biosynthesis of LDL-cholesterol (LDL).

Also as known to a person of ordinary skill in the art, endothelial cells and hepatocytes differ in their responses to molecular stimulation for activation of NF-kB and the genes transcriptionally regulated by NF-kB. For example, hepatocytes do not express VCAM-1 as a result of NF-kB activation.

Conclusion – Importantly, activation of NF-kB can be inhibited by antioxidants such as N-acetylcysteine.

Response - In Medford, this conclusion is limited specifically to the ability of NAC to prevent activation of NF-kB through the inhibition of the formation of ox-LDL from high LDL (hyperlipidemia) in endothelial cells and does not reflect the breath of information on NF-kB inhibition available to a person of ordinary skill in the art at the time of either the Medford filing (10/4/1994) or the filing of the instant application (10/31/2003). By the latter date, the prior art had repeatedly demonstrated (1) inhibition of NF-kB by antioxidants was a function of the activator or stimulation used; and (2) antioxidants were cell-specific in their ability to inhibit NF-kB activation.

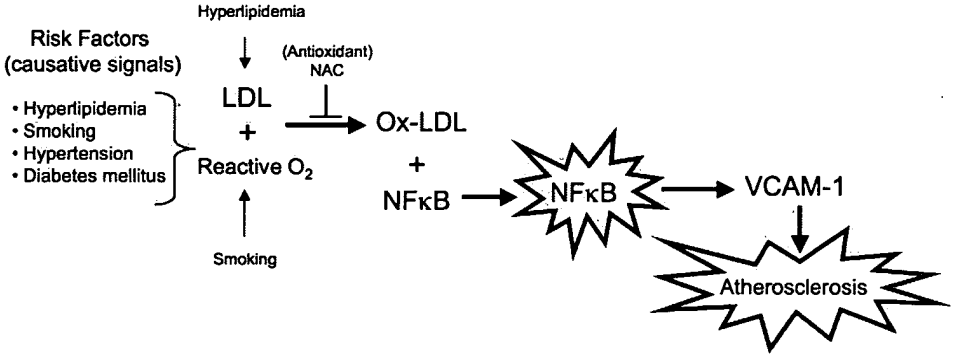
Medford [Col 2, lines 5-28] states:

> Although the precise biological signals that activate NF-kB are unknown, this transcriptional factor may integrate into a common molecular pathway many of the risk factors and "causative" signals of atherosclerosis such as hyperlipidemia, smoking, hypertension, and diabetes mellitus.
>
> Importantly, the activation of NF-kB in vascular endothelial cells by diverse signals can be specifically inhibited by antioxidants such as N-acetylcysteine and pyrrolidine dithiocarbamate (see U.S. Ser. No. 07/969,934), now allowed). This has led to the hypothesis that oxygen radicals play an important role in the activation of NF-kB through an undefined oxidation-reduction mechanism. Because an NF-kB enhancer element also regulates the transcription of the VCAM-1 promoter in an oxidation-reduction sensitive manner, oxidative stress in the atherosclerotic lesion may play a role in regulating VCAM-1 gene expression through this oxidation-reduction-sensitive transcriptional regulatory protein.
>
> It has been hypothesized that modification of low-density lipoprotein (LDL) into oxidatively modified LDL (ox-LDL) by reactive oxygen species is the central event that initiates and propagates atherosclerosis.

Taken as a whole, Medford presents a reactive oxygen species model of NF-kB activation in which ox-LDL functions as an intermediate in NF-kB activation and

describes NAC inhibition of VCAM-1 via an antioxidant mechanism to support their antioxidant treatment hypothesis for atherosclerosis. In this model, NAC would presumably function as an antioxidant and inhibit the formation of ox-LDL (not LDL), which would then not be available to activate NF-kB in endothelial cells (Figure 1).

Figure 1. A schematic representation of the link between hyperlipidemia and activation of nuclear factor kappa B (NF-kB) in endothelial cells expressing VCAM-1 as described by Medford [Col 2, lines 6-11].



In the model described by Medford and illustrated in Figure 1, hyperlipidemia is among the "causative signals" of atherosclerosis. The inhibition of NF-kB activation in this model is dependant on the inhibition of ox-LDL by an antioxidant in endothelial cells. As known to a person of ordinary skill in the art, it is believed that LDL (hyperlipidemia) is harmless until oxidized by free radicals, and it is postulated that *ingesting antioxidants and minimizing free radical exposure* may reduce LDL's contribution to atherosclerosis, though results are not conclusive.

By 1995, it was known in the art that, "the reactive oxygen model of NF-kB activation may be restricted to certain cell types, such as endothelial cells, and that the presence of such a system is not required for the activation of NF-kB by the cyokines IL-1 and TNF" as generally found in viral or bacterial infectious diseases [Brennan, P., and O'Neill, L. A. Effects of oxidants and antioxidants on nuclear factor kappa B activation in three different cell lines: evidence against a universal hypothesis involving oxygen radicals. *Biochim Biophys Acta* **1995**, *1260*, 167-75]. The same article demonstrated that NAC failed to inhibit NF-kB activation by IL-1 and TNF in EL4.NOB-1 (murine thymoma) and KB cells (human squamous cell carcinoma). The authors conclude, "these results and the divergence in the literature suggests that a model for NF-kB activation involving radicals is unlikely to be true for all cell types."

Later work demonstrated that not all antioxidants have the same effect on NF-kB [Rangan, G. K., Wang, Y., Tay, Y. C., and Harris, D. C. Inhibition of NFkappaB activation with antioxidants is correlated with reduced cytokine transcription in PTC. *Am J Physiol* **1999**, *277*, F779-89]. These authors also confirmed the inability of NAC to suppress NF-kB activation in lipopolysaccharide-stimulated PTC cells, while demonstrating a positive suppression of NF-kB activation by the antioxidants pyrrolidinedithiocarbamate and quercetin. Further, NAC demonstrated pro-oxidant effects and subsequent activation of NF-kB in A549 pulmonary cells indicating an association between exposure to reducing agents and activation of NF-kB in select cells [Das, K. C., Lewis-Molock, Y., and White, C. W. Activation of NF-kappa B and elevation of MnSOD gene expression by thiol reducing agents in lung adenocarcinoma (A549) cells. *Am J Physiol* **1995**, *269*, L588-602].

Finally, in 1992 the inability of NAC to reduce ox-LDL was demonstrated clinically in six, healthy human volunteers receiving 1.2 g NAC/day for four weeks followed by 2.4 g NAC/day for an additional two weeks [Kleinveld, H. A., Demacker, P. N., and Stalenhoef, A. F. Failure of N-acetylcysteine to reduce low-density lipoprotein oxidizability in healthy subjects. *Eur J Clin Pharmacol* **1992**, *43*, 639-42]. In conclusion, these authors wrote, "The results do not support the supposed antioxidative action of N-acetylcysteine. It seems more likely that N-acetylcysteine acts as a pro-oxidant in the dosage used." This clinical result stands in stark contrast to the in vitro teaching of Medford that administration of NAC would decrease ox-LDL via an antioxidant mechanism and draws into question the obviousness of using NAC clinically as an antioxidant to inhibit NF-kB activation via the inhibition of ox-LDL formation.

In addition to the reactive oxygen species model of NF-kB activation, NAC failed to inhibit NF-kB activation in models representative of chemical and infectious agents:

(1) in phorbol myristate acetate-stimulated CEM cells (T lymphocytic cell line) [Legrand-Poels, S., Zecchinon, L., Piret, B., Schoonbroodt, S., and Piette, J. Involvement of different transduction pathways in NF-kappa B activation by several inducers. *Free Radic Res* **1997**, *27*, 301-9]; (2) in *Theileria parva*-infected T cells [Palmer, G. H., Machado, J., Jr., Fernandez, P., Heussler, V., Perinat, T., and Dobbelaere, D. A. Parasite-mediated nuclear factor kappaB regulation in lymphoproliferation caused by Theileria parva infection. *Proc Natl Acad Sci U S A* **1997**, *94*, 12527-32]; and (3) in LPS-stimulated RAW 264.7 cells (murine macrophage)[Wadsworth, T. L., and Koop, D. R. Effects of the wine polyphenolics quercetin and resveratrol on pro-inflammatory cytokine expression in RAW 264.7 macrophages. *Biochem Pharmacol* **1999**, *57*, 941-9]. In the Wadsworth and Koop study, the antioxidants quercetin and resveratrol also failed to inhibit NF-kB activation. Thus, taken as a whole, NAC can function as both an antioxidant or pro-oxidant and antioxidants differ among themselves as to their ability to inhibit NF-kB activation.

Examiner's Summary - It would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted coenzyme Q10 in the composition as taught by McCleary with N-acetylcysteine as taught by Medford.

A person of ordinary skill in the art would have been motivated to make this substitution because: (1) of the functional equivalence of both coenzyme Q10 and N-acetylcysteineas well-known antioxidants; and (2) both McCleary and Medford are aimed at treating hyperlipidemia. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating hyperlipidemia with a composition comprising a conjugated linoleic acid and the antioxidant N-acetylcysteine.

Response - Regarding the functional equivalence of both coenzyme Q10 and N-acetylcysteineas as well-known antioxidants. While coenzyme Q10 and NAC can technically both be classified as antioxidants, it is incorrect to regard them as functionally equivalent. From their physical characteristics to their cellular distribution and activigty the two compounds are quite different and would not be characterized as functionally equivalent by a person of ordinary skill in the art for the following reasons: (1) coenzyme Q10 is lipid soluble with low bioavailability, while NAC is water-soluble and possess high bioavailability; (2) within cells coenzyme Q10 is found in membranes associated with the mitochondrial electron transport system; (3) the water-soluble NAC is found in the cytosolic fraction of cells and is rapidly utilized by cells as an intermediate in the synthesis of glutathione; and (4) as previously noted, NAC, as the doses suggested in the instant application, may function clinically as a pro-oxidant rather than an antioxidant [Kleinveld, H. A., Demacker, P. N., and Stalenhoef, A. F. Failure of N-acetylcysteine to reduce low-density lipoprotein oxidizability in healthy subjects. *Eur J Clin Pharmacol* **1992**, *43*, 639-42].

It was well-known by one of ordinary skill in the art at the time of the filing of the claimed invention that extrapolation of effects from one model system to another is not done with a reasonable expectation of similar results or success. For example, in the 3T3-L1 adipocyte, a model representative of the target tissue in the instant application, the anti-oxidant lipoic acid and NAC were tested for their ability to overcome glucose-stimulated insulin resistance. It was found that NAC did not prevent the development of glucose-induced insulin resistance in 3T3-L1 adipocytes, while lipoic acid did so successfully. Thus, with the demonstration that even closely associated antioxidants can perform differently in the same model, one skilled in the art would recognize the

difficulty in assuming the functional equivalence among antioxidants in different systems.

Response - That both McCleary and Medford are aimed at treating hyperlipidemia. While McCleary teaches a combination comprising CLA for the treatment of hyperlipidemia, at the time of the claimed invention seven of eight published clinical studies indicated a lack of effect of CLA on lowering blood lipids [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41]. The authors also conclude, "the evidence from human, short-term studies suggest that CLA supplementation does not reduce body fat or increase fat-free mass. There is evidence that CLA isomers sold as dietary supplements have marked biological effects, but there is accumulating evidence that the CLA t10,c12 isomer may adversely influence human health by producing lipodystrophy and insulin resistance."

As previously reviewed, it is clear that Medford is aimed at treating atherosclerosis and not aimed at treating hyperlipidemia. Medford teaches the use of NAC as an antioxidant to limit the formation of ox-LDL from LDL to prevent the expression of VCAM-1 in endothelial cells thus limiting the development of atherosclerosis. In this model, the LDL are present due to hyperlipidemia and there is no teaching to reduce LDL, rather the teaching is aimed at the reduction of ox-LDL.

Response – That one of ordinary skill in the art would have had a reasonable expectation of success in treating hyperlipidemia with a composition comprising a conjugated linoleic acid and the antioxidant N-acetylcysteine. As previously noted, in seven of eight clinical trials, CLA failed to positively effect blood lipid levels [reviewed in Larsen, T. M., Toubro, S., and Astrup, A. Efficacy and safety of dietary supplements containing CLA for

the treatment of obesity: evidence from animal and human studies. *J Lipid Res* **2003**, *44*, 2234-41], and in Medford, NAC was described as treating atherosclerosis not as a treatment for hyperlipidemia. Additionally, NAC had demonstrated a clinical failure for the purpose suggested by Meford, that of inhibition the formation of ox-LDL [Kleinveld, H. A., Demacker, P. N., and Stalenhoef, A. F. Failure of N-acetylcysteine to reduce low-density lipoprotein oxidizability in healthy subjects. *Eur J Clin Pharmacol* **1992**, *43*, 639-42]. For these reasons, one of ordinary skill in the art would not have had a reasonable expectation of success at the time of the instant application.

Examiner's Comment – "It is noted that the above paragraph describes the specific patient population that is claimed since abnormal fat maldistribution is defined as subcutaneous fat loss and body wasting from anti-retroviral treatment from an HIV-1 infection."

"Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have administered a composition comprising a conjugated linoleic acid and the antioxidant N-acetylcysteine, as taught by McCleary and Medford to a patient population with hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment from an HIV-1 infection because:

(1) Applicant's admission of the prior art teaches that HIV infection is accompanied by disturbances in lipid and glucose metabolism and that these metabolic abnormalities are further complicated by hypercholesterolemia and hypertriglyceridemia (both subgenus to hyperlipidemia) induced by anti-retroviral drugs; and

(2) Applicant's admission of the prior art teaches that it is estimated that almost two-thirds of HIV/AIDS patients exhibit abnormal fat maldistribution, which describe the

syndrome of body shape changes related to changes in fat distribution in people with HIV/AIDS receiving AR-therapy.

Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in treating a patient with hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment from an HIV-1 infection by administering a composition comprising a conjugated linoleic acid and N-acetylcysteine."

Response – At the time of the claimed invention, the use of CLA in the described patient population would not have resulted in an expected decrease in plasma lipids or gain in subcutaneous fat due to previously disclosed prior art describing no clinical effect of CLA on blood lipids in normal subjects and additional prior art describing the loss of adipose tissue, hepatomegaly, and development of lipodystrophy in mice administered CLA [Tsuboyama-Kasaoka, N., Takahashi, M., Tanemura, K., Kim, H. J., Tange, T., Okuyama, H., Kasai, M., Ikemoto, S., and Ezaki, O. Conjugated linoleic acid supplementation reduces adipose tissue by apoptosis and develops lipodystrophy in mice. *Diabetes* **2000**, *49*, 1534-42]. Considering the prior art, one of ordinary skill would consider CLA to be potentially harmful to the patient population.

Prior art also teaches that a 24-week antioxidant supplementation including NAC increased fasting glucose, insulin and HOMA (homeostasis model assessment) scores reflecting an increased insulin resistance and had no effect on LDL, HDL or triglycerides in HIV-infected subjects with lipoatrophy[McComsey, G., Southwell, H., Gripshover, B., Salata, R., and Valdez, H. Effect of antioxidants on glucose metabolism and plasma lipids in HIV-infected subjects with lipoatrophy. *J Acquir Immune Defic Syndr* **2003**, *33*, 605-7]. Taken together these references indicate that the use of CLA in the disclosed patient population would be expected, by

one of ordinary skill in the art, to be potentially harmful and any beneficial effect of CLA either alone or in a combination with NAC in the patient population would be an unexpected result. Additionally, the prior art references when combined do not teach or suggest the claim limitation of hyperlipidemia coincident with subcutaneous fat loss (lipodystrophy).

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

The requested declaration under 37 CFR § 1.132 to compare the claimed subject matter with the closet prior art in order to effectively to rebut a prima facie case of obviousness is enclosed. The declaration also explains how the results presented should be taken to be unexpected and significant.

SUMMARY

In summary, Applicant's present a review of the three basic criteria that must be met in order to establishing a *prima facie* case of obvious along with a summation of their previous responses:

(A) THERE MUST BE SOME SUGGESTION OR MOTIVATION, EITHER IN THE REFERENCES THEMSELVES OR IN THE KNOWLEDGE GENERALLY AVAILABLE TO ONE OF ORDINARY SKILL IN THE ART, TO MODIFY THE REFERENCE TEACHINGS.

1. There was no suggestion or motivation for person of ordinary skill in the art to combine the teaching of McCleary with the that of Medford and substitute NAC for coenzyme Q10 in combination with CLA for the treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject by administering triglyceride of CLA and NAC for the following reasons.

i. Medford did not teach the treatment of hyperlipidemia.

ii. The prior art at the time of the instant application does not teach the functional equivalence of NAC and coenzyme Q10 in adipocytes or in any other relevant, cellular or in vivo model. Rather the prior art discloses the clinical failure of NAC to perform as a functional antioxidant to prevent the formation of ox-LDL from LDL and the lack of functional equivalence of the closely related NAC and lipoic acid.

iii. The preponderance of literature (seven of eight clinical trials) indicated that CLA had no effect of hyperlipidemia.

iv. At the time of the claimed invention, it was known in the art that CLA supplementation induced lipodystrophy in mice.

v. It was known at the time of the instant invention, that clinical use of NAC and antioxidants increased plasma glucose and insulin, and had no effect on plasma lipids in HIV-infected subjects with lipodystrophy while receiving anti-retroviral therapy.

(B) THERE MUST BE A REASONABLE EXPECTATION OF SUCCESS.

1. At the time of the claimed invention, a person of ordinary skill in the art would not have had a reasonable expectation of success to substitute NAC for coenzyme Q10 in combination with CLA for the treating or normalizing hyperlipidemia coincident with subcutaneous fat loss and body wasting resulting from anti-retroviral treatment of HIV-1 infection in a subject by administering triglyceride of CLA and NAC for the following reasons:

i. Medford teaches antioxidant effects of NAC in vascular endothelial cells to inhibit the formation of ox-LDL from LDL (hyperlipidemia) to treat

atherosclerosis. Vascular endothelial cells are not the target cells in the claimed invention, adipocytes are the target cells. At the time of the claimed invention, a person of ordinary skill in the art understood that adipocytes do not respond to antioxidants in the same way as endothelial cells and similar antioxidant such as lipoic acid and NAC respond differently in the adipocyte model.

ii. At the time of the claimed invention, a clinical trail has established that NAC did not inhibit the formation of ox-LDL and functioned as a pro-oxidant at the doses suggested in the instant application.

iii. At the time of the claimed invention, it was known in the art that CLA supplementation induced lipodystrophy in mice.

iv. At the time of the claimed invention, it was known that clinical use of NAC and antioxidants increased plasma glucose and insulin, and had no effect on plasma lipids in HIV-infected subjects with lipodystrophy while receiving anti-retroviral therapy.

(C) FINALLY, THE PRIOR ART REFERENCES WHEN COMBINED MUST TEACH OR SUGGEST ALL THE CLAIM LIMITATIONS.

1. The prior art reference Medford et al. does not teach the treatment of hyperlipidemia. Rather Medford teaches the treatment of atherosclerosis with NAC to inhibit the formation of ox-LDL in the presence of hyperlipidemia and free radicals in vascular endothelial cells. Medford teaches that hyperlipidemia is a risk factor for atherosclerosis along with other risk factors such as smoking, diabetes and hypertension that, in combination generate ox-LDL. In Medford, it is taught that NAC functions as an antioxidant to inhibit the formation of ox-LDL from LDL. No teaching is presented to

enable the use of NAC to prevent the increase in synthesis of LDL at its source of biosynthesis in the liver.

2. The prior art at the time of the instant application does not teach the functional equivalence of NAC and coenzyme Q10 in adipocytes or in any other relevant, cellular or in vivo model. Rather the prior art discloses the clinical failure of NAC to perform as a functional antioxidant and the lack of functional equivalence of the closely related NAC and lipoic acid.

3. The prior art does not teach the successful use of CLA or NAC for the treatment of hyperlipidemia in HIV-1 persons exhibiting lipodystrophy during treatment with anti-retroviral drugs. Teachings available in the prior art demonstrated that clinical CLA supplementation had no effect on blood lipids and that NAC and antioxidants increased blood glucose and insulin, and had no effect on blood lipids in persons with HIV-1 exhibiting lipodystrophy while receiving anti-retroviral therapy.

In view of the foregoing, the Applicants assert that Claims 21-24 and 32-35 of the present application present allowable subject matter and the allowance thereof are requested. If any impediment to the allowance of these claims remains after consideration of the present amendment and above remarks, and such impediment could be removed during a telephone interview, the Examiner is invited to telephone Dr. John G. Babish so that such issues may be resolved as expeditiously as possible.

Dated this 27th day of October, 2008.

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